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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,356	05/03/2001	Donald Morris	032775-041	6890

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FISH & RICHARDSON P.C.
3300 DAIN RAUSCHER PLAZA
MINNEAPOLIS, MN 55402

EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/847,356	MORRIS ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/24/2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,19 and 25-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,19 and 25-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/30/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Claims 18, 19 and 25-49 are pending.

Claims 18 and 19 have been amended.

Claims 38-49 have been added.

Claims 18, 19 and 25-49 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections

Claim Rejections - 35 USC § 103

3. The rejection of claims 18, 25, 27-31 and 37 under 35 U.S.C. 103(a) as being unpatentable Coffey et al. (Science 282: 1332-1334, November 13, 1998/ IDS reference), in view of Freshney (Culture of Animal Cells: A Manual of Basic Technique, second edition, New York, NY, 1987) is withdrawn.

4. The rejection of claims 18, 25-29 and 31 under 35 U.S.C. 103(a) as being unpatentable Coffey et al. (Science 282: 1332-1334, November 13, 1998/ IDS reference), in view of U.S. Patent number 6,136,307 (filed February 24, 1999/ IDS reference) is withdrawn.

5. The rejection of claims 18, 19 and 25-37 under 35 U.S.C. 103(a) as being unpatentable Coffey et al. (Science 282: 1332-1334, November 13, 1998/ IDS reference), in view of U.S. Patent number 5,861,159 (January 19, 1999), Freshney (Culture of Animal Cells: A Manual of Basic Technique, second edition, New York, NY, 1987) and U.S. Patent number 6,136,307 (filed February 24, 1999/ IDS reference) is withdrawn.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

6. Claims 18, 19, 25, 27-32, 34-40, 43-46 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gulati (Journal of Hematotherapy 2:467-471, 1993), in view of Coffey et al. (Science 282: 1332-1334, November 13, 1998/ IDS reference) and Freshney (Culture of Animal Cells: A Manual of Basic Technique, second edition, New York, NY, 1987). Gulati teaches "[t]he success of autologous stem cell transplantation using bone marrow or peripheral blood stem cells..." and suggests "[v]arious methods... for removing (purging)...contaminants", see abstract. Gulati explains that the "[*e*]*x vivo* purging can be achieved by negative selection in which the tumor cells are eliminated, or by positive selection", see page 468, column 1, Purging techniques section. Gulati also teaches the applicability of contaminant removal from *in vivo* and *in vitro* models utilizing cell lines and fresh cancer cells in concert with antibody and complement-mediated purging, see column 468, column 2, Proof of Clinical...section.

Gulati does not teach a method of preparing a cellular composition for autologous transplantation into a recipient comprising contacting the composition with a reovirus *ex vivo* to result in oncolysis of ras-mediated neoplastic cells and the administration of anti-reovirus antibodies, nor the step of freezing and storing the reovirus-treated composition in a solution containing dimethyl sulfoxide (DMSO).

However, Coffey teaches a method of oncolysis of a cellular composition consisting of ras-transformed C3H-10T1/2 fibroblast tumors mediated by intratumoral injections of reovirus serotype 3 (strain Dearing) and the subsequent complete regression of tumors, see page 1333, bridging paragraph of columns 2 and 3; page 1334, Figure 4B. Coffey also teaches a method of oncolysis of a ras-mediated human brain glioblastoma cell line, U-87 tumor implanted into the hind flank of SCID mice, see bridging paragraph of pages 1332 and 1333. Coffey notes that "...the human glioblastoma U87 cell line overexpresses the PDGFR and thus has increased levels of activated Ras", hence the Examiner regards the formed tumor as a ras-mediated neoplasm, see page 1332, column 3, paragraph 2. Treatment with the Dearing strain of reovirus serotype 3 resulted in "[n]ecrosis of tumor cells was due to direct lysis by the virus...".

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare a cellular composition contacted with a oncolytic reovirus for purging of tumor cells and subsequent autologous transplantation because Gulati sets forth proof of clinical benefits of purging techniques, see page 468, column 2, Proof of Clinical...section. One of ordinary skill in the art would have been

motivated to utilize the teachings of all the references with a reasonable expectation of success by teachings of both Gulati and Coffey. With particularity the Coffey article teaches that (1) "[t]he selective replication of reovirus in cells with an activated replication of reovirus in cells with an activated Ras signaling pathway, coupled with the relatively nonpathogenic nature of [the] virus in humans...makes it attractive as a potential oncolytic agent and (2) "[t]he results from the C3H mouse model...suggest the feasibility of using this treatment in humans", see page 1332, column 3, last sentence of bridging paragraph and page 1334, column 1, last sentence, respectively. These observations support the use of reovirus *ex vivo* within a cellular composition for autologous transplantation in light of the successful syngeneic transplantation process and established methodology of autologous stem cell transplantation resulting in better hematopoietic engraftment and lower relapse rate.

However, Gulati teaches that "[f]ollowing antibody...mediated purging...marrows were found to be [tumor free]..." and with consequent reduced relapses. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to supplement the ex vivo reovirus cellular composition with an additional anti-tumor agent in order to rid the cell population of cancer cells. One of ordinary skill in the art would have been motivated to utilize the teachings of all the references with a reasonable expectation of success by teachings of both Gulati and Coffey.

Furthermore, Freshney teaches the storage of a "seed stock" in helping to ensure it remains free of contamination and readily available. It would have been *prima facie*

obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare a oncolytic viral composition in a solution containing DMSO and preserving a "seed stock". One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings of Freshney that cryopreserving "seed stock" is a general practice implemented in cell biology to make certain there is continued availability of the selected stock.

7. Claims 18, 19, 25-29, 31-36, and 38-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gulati (Journal of Hematotherapy 2:467-471, 1993), in view of Coffey et al. (Science 282: 1332-1334, November 13, 1998/ IDS reference) and U.S. Patent number 6,136,307 (filed February 24, 1999/ IDS reference). Gulati teaches "[t]he success of autologous stem cell transplantation using bone marrow or peripheral blood stem cells..." and suggests "[v]arious methods... for removing (purging)...contaminants", see abstract. Gulati explains that the "[*e*]*x vivo* purging can be achieved by negative selection in which the tumor cells are eliminated, or by positive selection", see page 468, column 1, Purging techniques section. Gulati also teaches the applicability of contaminant removal from *in vivo* and *in vitro* models utilizing cell lines and fresh cancer cells in concert with antibody and complement-mediated purging, see column 468, column 2, Proof of Clinical...section.

Gulati does not teach a method of preparing a cellular composition for autologous transplantation into a recipient comprising contacting the composition with a reovirus *ex vivo* to result in oncoloysis of ras-mediated neoplastic cells, wherein the

reovirus is an avian reovirus cells, the administration of anti-reovirus antibodies and the cellular composition comprises a tissue, an organ or any portion of a tissue or an organ.

However, Coffey teaches a method of oncolysis of a cellular composition consisting of ras-transformed C3H-10T1/2 fibroblast tumors mediated by intratumoral injections of reovirus serotype 3 (strain Dearing) and the subsequent complete regression of tumors, see page 1333, bridging paragraph of columns 2 and 3; page 1334, Figure 4B. Coffey also teaches a method of oncolysis of a ras-mediated human brain glioblastoma cell line, U-87 tumor implanted into the hind flank of SCID mice, see bridging paragraph of pages 1332 and 1333. Coffey notes that "...the human glioblastoma U87 cell line overexpresses the PDGFR and thus has increased levels of activated Ras", hence the Examiner regards the formed tumor as a ras-mediated neoplasm, see page 1332, column 3, paragraph 2. Treatment with the Dearing strain of reovirus serotype 3 resulted in "[n]ecrosis of tumor cells was due to direct lysis by the virus...".

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare a cellular composition contacted with a oncolytic reovirus for purging of tumor cells and subsequent autologous transplantation because Gulati sets forth proof of clinical benefits of purging techniques, see page 468, column 2, Proof of Clinical...section. One of ordinary skill in the art would have been motivated to utilize the teachings of all the references with a reasonable expectation of success by teachings of both Gulati and Coffey. With particularity the Coffey article teaches that (1) "[t]he selective replication of reovirus in cells with an activated

replication of reovirus in cells with an activated Ras signaling pathway, coupled with the relatively nonpathogenic nature of [the] virus in humans...makes it attractive as a potential oncolytic agent and (2) "[t]he results from the C3H mouse model...suggest the feasibility of using this treatment in humans", see page 1332, column 3, last sentence of bridging paragraph and page 1334, column 1, last sentence, respectively. These observations support the use of reovirus *ex vivo* within a cellular composition for autologous transplantation in light of the successful syngeneic transplantation process and established methodology of autologous stem cell transplantation resulting in better hematopoietic engraftment and lower relapse rate.

However, Gulati teaches that "[f]ollowing antibody...mediated purging...marrows were found to be [tumor free]..." and with consequent reduced relapses. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to supplement the ex vivo reovirus cellular composition with an additional anti-tumor agent in order to rid the cell population of cancer cells. One of ordinary skill in the art would have been motivated to utilize the teachings of all the references with a reasonable expectation of success by teachings of both Gulati and Coffey.

Furthermore, U.S. patent #6,136,307 teaches that a variety of solid neoplasms and hematopoietic neoplasms can be treated and non-human mammalian reoviruses such as an avian reovirus can be used, see abstract; column 6, lines 45-51; bridging paragraph of columns 7 and 8; column 8, lines 19-32. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to

treat both solid (i.e. liver, lung, pancreatic islet cells) and hematopoietic neoplasms (i.e. whole blood), as well as use an avian reovirus to mediate oncolysis. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Coffey and the patent that suggests that either solid neoplasms or malignant tumors can be treated alternatively with an avian reovirus, see column 6, lines 37-51; bridging paragraph of columns 7 and 8; column 8, lines 42-56.

8. Claims 18, 19 and 25-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gulati (Journal of Hematotherapy 2:467-471, 1993), in view of Coffey et al. (Science 282: 1332-1334, November 13, 1998/ IDS reference), U.S. Patent number 5,861,159 (January 19, 1999), Freshney (Culture of Animal Cells: A Manual of Basic Technique, second edition, New York, NY, 1987) and U.S. Patent number 6,136,307 (filed February 24, 1999/ IDS reference).

Gulati teaches "[t]he success of autologous stem cell transplantation using bone marrow or peripheral blood stem cells..." and suggests "[v]arious methods... for removing (purging)...contaminants", see abstract. Gulati explains that the "[*e*]*x vivo* purging can be achieved by negative selection in which the tumor cells are eliminated, or by positive selection", see page 468, column 1, Purging techniques section. Gulati also teaches the applicability of contaminant removal from *in vivo* and *in vitro* models utilizing cell lines and fresh cancer cells in concert with antibody and complement-mediated purging, see column 468, column 2, Proof of Clinical...section.

Gulati does not teach a method of preparing a cellular composition for autologous transplantation into a recipient comprising contacting the composition with a reovirus *ex vivo* to result in oncoloysis of ras-mediated neoplastic cells, wherein the reovirus is an avian reovirus, the administration of immune system stimulating agents and the cellular composition comprises a tissue, an organ or any portion of a tissue or an organ. Nor does Gulati teach the step of freezing and storing the reovirus-treated composition in a solution containing dimethyl sulfoxide (DMSO).

However, Coffey teaches a method of oncolysis of a cellular composition consisting of ras-transformed C3H-10T1/2 fibroblast tumors mediated by intratumoral injections of reovirus serotype 3 (strain Dearing) and the subsequent complete regression of tumors, see page 1333, bridging paragraph of columns 2 and 3; page 1334, Figure 4B. Coffey also teaches a method of oncolysis of a ras-mediated human brain glioblastoma cell line, U-87 tumor implanted into the hind flank of SCID mice, see bridging paragraph of pages 1332 and 1333. Coffey notes that "...the human glioblastoma U87 cell line overexpresses the PDGFR and thus has increased levels of activated Ras", hence the Examiner regards the formed tumor as a ras-mediated neoplasm, see page 1332, column 3, paragraph 2. Treatment with the Dearing strain of reovirus serotype 3 resulted in "[n]ecrosis of tumor cells was due to direct lysis by the virus...".

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare a cellular composition contacted with a oncolytic reovirus for autologous transplantation because Gulati sets forth proof of

clinical benefits of purging techniques, see page 468, column 2, Proof of Clinical...section. One of ordinary skill in the art would have been motivated to utilize the teachings of all the references with a reasonable expectation of success by teachings of both Gulati and Coffey. With particularity the Coffey article teaches that (1) "[t]he selective replication of reovirus in cells with an activated replication of reovirus in cells with an activated Ras signaling pathway, coupled with the relatively nonpathogenic nature of [the] virus in humans...makes it attractive as a potential oncolytic agent and (2) "[t]he results from the C3H mouse model...suggest the feasibility of using this treatment in humans", see page 1332, column 3, last sentence of bridging paragraph and page 1334, column 1, last sentence, respectively. These observations support the use of reovirus *ex vivo* within a cellular composition for autologous transplantation in light of the successful syngeneic transplantation process and established methodology of autologous stem cell transplantation resulting in better hematopoietic engraftment and lower relapse rate.

Furthermore, U.S. Patent #5,861,159 teaches a method of stimulating a systemic immune response to a tumor cell by administering a sustained release of therapeutic compounds to allow a host immune system to ameliorate local as well as metastatic tumors in a host. The immunopotentiating agent may be a cytokine such as tumor necrosis factor, GM-CSF, interleukin or interferon, see abstract and column 3, Summary of the Invention section. Immune system stimulating agents taught in the said patent would be effective in preventing tumor growth, tumor metastasis and tumor regression in a subject. It would have been *prima facie* obvious to one of ordinary skill in the art at

the time the claimed invention was made to implement the teachings of all the references in the method of preparing a cellular composition including immune system stimulating agents for autologous transplantation in order to destroy the neoplastic cells. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings well known in the art the manufacture of anti-tumor medicaments incorporating anti-cancer agents is efficacious for the in vivo treatment of cancer and the potentiation of a subjects' immune response.

Additionally, U.S. patent #6,136,307 teaches that a variety of solid neoplasms and hematopoietic neoplasms can be treated and non-human mammalian reoviruses such as an avian reovirus can be used, see abstract; column 6, lines 45-51; bridging paragraph of columns 7 and 8; column 8, lines 19-32. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to treat both solid (i.e. liver, lung, pancreatic islet cells) and hematopoietic neoplasms (i.e. whole blood), as well as use an avian reovirus to mediate oncolysis. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in the patent that suggests that either solid neoplasms or malignant tumors can be treated alternatively with an avian reovirus, see column 6, lines 37-51; bridging paragraph of columns 7 and 8; column 8, lines 42-56.

Moreover, Freshney teaches the storage of a "seed stock" in helping to ensure it remains free of contamination and readily available. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare a oncolytic viral composition in a solution containing DMSO and preserving a

"seed stock". One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings of Freshney that cryopreserving "seed stock" is a general practice in cell biology to make certain there is continued availability of the selected stock.

9. Claims 18, 25-29 and 38-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nordon et al. (Artificial Organs 20(5): 396-402, May 1996), in view of Coffey et al. (Science 282: 1332-1334, November 13, 1998/ IDS reference) and and U.S. Patent number 6,136,307 (filed February 24, 1999/ IDS reference). Nordon establishes well known, as well as art known methodologies of ex vivo expansion technology for the development of new cellular products for the treatment of cancer, see title and abstract. Nordon teaches a general scheme for processing mononuclear cells collected from blood, bone marrow or cord blood in order to enrich a target cell population for the elimination of tumor cells. "Cell depletion or enrichment strategies may be used to purge tumor cells from autologous grafts", see page 397, column 2, first sentence of first complete paragraph. Nordon also states that "[s]torage of stem cells and lymphocytes for later therapy or processing is possible using cryopreservation techniques, see page 396, bridging paragraph of columns 1 and 2 and Figure 1 on page 397.

Nordon does not teach a method of preparing a cellular composition for autologous transplantation into a recipient comprising contacting the composition with a reovirus *ex vivo* to result in oncoloysis of ras-mediated neoplastic cells, wherein the reovirus is an

avian reovirus and the cellular composition comprises a tissue, an organ or any portion of a tissue or an organ.

However, Coffey teaches a method of oncolysis of a cellular composition consisting of ras-transformed C3H-10T1/2 fibroblast tumors mediated by intratumoral injections of reovirus serotype 3 (strain Dearing) and the subsequent complete regression of tumors, see page 1333, bridging paragraph of columns 2 and 3; page 1334, Figure 4B. Coffey also teaches a method of oncolysis of a ras-mediated human brain glioblastoma cell line, U-87 tumor implanted into the hind flank of SCID mice, see bridging paragraph of pages 1332 and 1333. Coffey notes that "...the human glioblastoma U87 cell line overexpresses the PDGFR and thus has increased levels of activated Ras", hence the Examiner regards the formed tumor as a ras-mediated neoplasm, see page 1332, column 3, paragraph 2. Treatment with the Dearing strain of reovirus serotype 3 resulted in "[n]ecrosis of tumor cells was due to direct lysis by the virus...".

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare a cellular composition contacted with a oncolytic reovirus for autologous transplantation because Nordon provides the impetus to one of ordinary skill in the art to develop novel cell-based therapies for the treatment of malignancy and sets forth proof that ex vivo manipulation of cell subsets is routine in the art. One of ordinary skill in the art would have been motivated to utilize the teachings of all the references with a reasonable expectation of success by teachings of both Nordon and Coffey. With particularity the Coffey article teaches that (1) "[t]he

selective replication of reovirus in cells with an activated replication of reovirus in cells with an activated Ras signaling pathway, coupled with the relatively nonpathogenic nature of [the] virus in humans...makes it attractive as a potential oncolytic agent and (2) "[t]he results from the C3H mouse model...suggest the feasibility of using this treatment in humans", see page 1332, column 3, last sentence of bridging paragraph and page 1334, column 1, last sentence, respectively. These observations support the use of reovirus *ex vivo* within a cellular composition for autologous transplantation in light of the successful syngeneic transplantation process and established methodology of autologous stem cell transplantation resulting in better hematopoietic engraftment and lower relapse rate.

Furthermore, U.S. patent #6,136,307 teaches that a variety of solid neoplasms and hematopoietic neoplasms can be treated and non-human mammalian reoviruses such as an avian reovirus can be used, see abstract; column 6, lines 45-51; bridging paragraph of columns 7 and 8; column 8, lines 19-32. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to treat both solid (i.e. liver, lung, pancreatic islet cells) and hematopoietic neoplasms (i.e. whole blood), as well as use an avian reovirus to mediate oncolysis. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in the references and the patent that suggests that either solid neoplasms or malignant tumors can be treated alternatively with an avian reovirus, see column 6, lines 37-51; bridging paragraph of columns 7 and 8; column 8, lines 42-56.

10. Claims 18, 19 and 25-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nordon et al. (Artificial Organs 20(5): 396-402, May 1996), in view of Coffey et al. (Science 282: 1332-1334, November 13, 1998/ IDS reference), U.S. Patent number 5,861,159 (January 19, 1999) and U.S. Patent number 6,136,307 (filed February 24, 1999/ IDS reference).

Nordon establishes well known, as well as art known methodologies of ex vivo expansion technology for the development of new cellular products for the treatment of cancer, see title and abstract. Nordon teaches a general scheme for processing mononuclear cells collected from blood, bone marrow or cord blood in order to enrich a target cell population for the elimination of tumor cells. "Cell depletion or enrichment strategies may be used to purge tumor cells from autologous grafts", see page 397, column 2, first sentence of first complete paragraph. Nordon also states that "[s]torage of stem cells and lymphocytes for later therapy or processing is possible using cryopreservation techniques, see page 396, bridging paragraph of columns 1 and 2 and Figure 1 on page 397.

Nordon does not teach a method of preparing a cellular composition for autologous transplantation into a recipient comprising contacting the composition with a reovirus *ex vivo* to result in oncoloysis of ras-mediated neoplastic cells, wherein the reovirus is an avian reovirus, the administration of immune system stimulating agents and the cellular composition comprises a tissue, an organ or any portion of a tissue or an organ.

However, Coffey teaches a method of oncolysis of a cellular composition consisting of ras-transformed C3H-10T1/2 fibroblast tumors mediated by intratumoral injections of reovirus serotype 3 (strain Dearing) and the subsequent complete regression of tumors, see page 1333, bridging paragraph of columns 2 and 3; page 1334, Figure 4B. Coffey also teaches a method of oncolysis of a ras-mediated human brain glioblastoma cell line, U-87 tumor implanted into the hind flank of SCID mice, see bridging paragraph of pages 1332 and 1333. Coffey notes that "...the human glioblastoma U87 cell line overexpresses the PDGFR and thus has increased levels of activated Ras", hence the Examiner regards the formed tumor as a ras-mediated neoplasm, see page 1332, column 3, paragraph 2. Treatment with the Dearing strain of reovirus serotype 3 resulted in "[n]ecrosis of tumor cells was due to direct lysis by the virus...".

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare a cellular composition contacted with a oncolytic reovirus for autologous transplantation because Nordon provides the impetus to one of ordinary skill in the art to develop novel cell-based therapies for the treatment of malignancy and sets forth proof that ex vivo manipulation of cell subsets is routine in the art. One of ordinary skill in the art would have been motivated to utilize the teachings of all the references with a reasonable expectation of success by teachings of both Nordon and Coffey. With particularity the Coffey article teaches that (1) "[t]he selective replication of reovirus in cells with an activated replication of reovirus in cells with an activated Ras signaling pathway, coupled with the relatively nonpathogenic

nature of [the] virus in humans...makes it attractive as a potential oncolytic agent and (2) "[t]he results from the C3H mouse model...suggest the feasibility of using this treatment in humans", see page 1332, column 3, last sentence of bridging paragraph and page 1334, column 1, last sentence, respectively. These observations support the use of reovirus *ex vivo* within a cellular composition for autologous transplantation in light of the successful syngeneic transplantation process and established methodology of autologous stem cell transplantation resulting in better hematopoietic engraftment and lower relapse rate.

Furthermore, U.S. Patent #5,861,159 teaches a method of stimulating a systemic immune response to a tumor cell by administering a sustained release of therapeutic compounds to allow a host immune system to ameliorate local as well as metastatic tumors in a host. The immunopotentiating agent may be a cytokine such as tumor necrosis factor, GM-CSF, interleukin or interferon, see abstract and column 3, Summary of the Invention section. Immune system stimulating agents taught in the said patent would be effective in preventing tumor growth, tumor metastasis and tumor regression in a subject. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to implement the teachings of all the references in the method of preparing a cellular composition including immune system stimulating agents for autologous transplantation in order to destroy the neoplastic cells. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings well known in the art the manufacture of anti-tumor

medicaments incorporating anti-cancer agents is efficacious for the in vivo treatment of cancer and the potentiation of a subjects' immune response.

Additionally, U.S. patent #6,136,307 teaches that a variety of solid neoplasms and hematopoietic neoplasms can be treated and non-human mammalian reoviruses such as an avian reovirus can be used, see abstract; column 6, lines 45-51; bridging paragraph of columns 7 and 8; column 8, lines 19-32. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to treat both solid (i.e. liver, lung, pancreatic islet cells) and hematopoietic neoplasms (i.e. whole blood), as well as use an avian reovirus to mediate oncolysis. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in the patent that suggests that either solid neoplasms or malignant tumors can be treated alternatively with an avian reovirus, see column 6, lines 37-51; bridging paragraph of columns 7 and 8; column 8, lines 42-56.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571)272-0831. The examiner works a flexible schedule, however can normally be reached between the hours of 7:00 am to 4:30 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne "Bonnie" Eyler, Ph.D. can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
01 April 2004